Post-marketing Surveillance Study to Evaluate the Efficacy and Safety for the Combination of Cinnarizine and Dimenhydrinate in Indian Patients of Vertigo

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ABSTRACT

Introduction: Vertigo is a medical condition in which patient has the sensation of moving of surrounding objects when they are not which can also be associated with vomiting, nausea, difficulties in walking or sweating. It is considered that the Cinnarizine and Dimenhydrinate has the synergistic effect for the treatment of Vertigo due to their calcium antagonist and antihistaminic action respectively. This post marketing surveillance study was conducted to test the efficacy and safety for the combination of Cinnarizine and Dimenhydrinate in Indian patients of Vertigo.

Material and methods: Total 200 trial subjects were recruited for the study. All recruited trial subjects were asked to take the investigational product for 5 days in the dose of 1 tablet twice a day. Efficacy assessment was done by vertigo symptom score (VSS) which was measured on VSS scale ranging from 0 to 10 where 0 was no symptom to 10 was the maximum tolerated symptoms. Safety assessment was done by the reported adverse events.

Results: Out of 200, 171 trial subjects completed the study. VSS was 6.69 on day 1 which was reduced to 3.28, reduction of 51% on day 3 which further reduced to 0.87, reduction of 86.98% on day 5. Significant reduction of VSS was found in the clinical trial duration of 5 days in all trial subjects. Also no serious or unexpected adverse event was found to be reported.

Conclusion: The fixed dose combination of Cinnarizine 20mg and Dimenhydrinate 40mg per tablet was found efficacious and safe for the treatment of Vertigo.

Keywords: Vertigo, Cinnarizine, Dimenhydrinate

INTRODUCTION

Vertigo is an unpleasant or incorrect perception of movement or a feeling of the sense of motion when there is no motion in relation to the earth's gravity or movement in one's own body, such as swaying or rotation. Vertigo is subtype of dizziness resulted from vestibular imbalance.[1] The circumstances leading to an episode of vertigo helps to determine the cause of the episode. Vertigo is usually caused by rapid head movements because they amplify any imbalances in the vestibular pathways. Sweating, nausea, whiteness and vomiting are typical autonomic symptoms of vertigo.[2] Vertigo can last anywhere from a few hours to several days and can cause serious dysfunction in patients, leading to significant limitations in everyday activities and result in a lowering of health-related quality of life.[1,3] Vertigo can be treated with antihistamines, calcium antagonists, histamine analogues (eg, betahistine derivatives), diuretics, neuroleptics as well as other psychotherapeutic medications, corticosteroids agents and hemorheologics. As vertigo is related to dysfunction of vestibular system in which homeostatic of calcium is disrupted and it also added with effects of histamine as well as cholinergic receptors. Hence combination of two antihistamines can be used to treat the vestibular dysfunction by inhibition of calcium influx and inhibition of histamine and cholinergic receptors. Cinnarizine, a selective calcium-channel blocker and Dimenhydrinate, a H 1 antihistamine can be used in combination for the treatment of vertigo.[4]

Cinnarizine is a well-known anti-vertigo drug that was originally formulated as an anti-histaminic drug. It is a chemical compound that is made up of 1-benzhydryl 1-4-cinnamyl piperazine. It acts as a calcium channel blocker and a histamine H1 antagonist. It binds to both the histamine H1 and muscarinic acetylcholine receptors. Cinnarizine prevents vascular smooth muscle cell contractions by blocking calcium channels. It can be used to treat vertigo and Meniere's disease, nausea, vomiting, and motion sickness, as well as other vestibular symptoms.[5,6]

Dimenhydrinate is an antihistamine acts by reducing the effects of histamine.[7] Diphenhydramine works as an inverse agonist at the H1 receptor, reverses histamine's effects on capillaries and reduces allergic reaction symptoms. It easily passes the blood-brain barrier and inversely agonises H1 CNS receptors which may cause patient to feel drowsiness and may suppress the medullary cough core.[8,9]

The rationale of using the combination of an antihistamine (Dimenhydrinate) and a calcium channel blocker (Cinnarizine) for symptomatic relief of vertigo derives from their mechanisms of action as both are antihistaminic

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drugs. Dimenhydrinate works primarily on the central vestibular system by inhibiting the actions of histamine and cholinergic receptors in the vestibular nuclei and vomiting area. Cinnarizine prevents calcium influx into vestibular hair cells, regulates hair-cells afferent vestibular transmission, and thus exerts its anti-vertigo effects mainly on the peripheral vestibular system.[10] This study was conducted to generate more data on efficacy and safety for the fixed dose combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg per tablet (Investigational product) in the treatment of vertigo in Indian Population.

MATERIAL AND METHODS

This was a multicentric, open-label, non-comparative, user-initiated post marketing surveillance (PMS) study that was conducted at 12 clinical trial sites across India. A total of 180 trial subjects were enrolled for the study by the investigators all across India.

Inclusion and Exclusion criteria

Trial subjects with a confirmed diagnosis of vertigo of both the genders including male and female of age between 18 to 75 years, who were ready to sign the informed consent form and willing to stick to the study protocol were recruited for the post marketing surveillance study.

Trial subjects with hypersensitivity to the individual study drug present in the investigational product were excluded from the study. Pregnant and lactating women were excluded from this study. Trial subjects who could not adhere to protocol including but not limited to psychologically imbalanced or mentally ill patients were also excluded from the PMS study.

Study design

The study was conducted at total 12 clinical trial sites and total 180 trial subjects were recruited for the post marketing surveillance study out of which 171 trial subjects completed the study as per the study procedure. The study design was of non-comparative, non-randomized, user initiated and open label nature. All investigators, research staff and trial subjects or any other people either from the side of investigator, trial subject or the sponsor involved in the study were aware of the investigational product and its composition.

Study Procedure

According to the inclusion and exclusion criteria all trial subjects were enrolled for the PMS study by the investigator. The information of PMS study and Investigational product was provided to trial subject by the investigator. Trial subjects shortlisted for the study were well informed about the study by the investigator and if agreed then and then only they were asked to sign the informed consent form and were recruited for the study. Investigator also cleared all the questions and doubts of the recruited trial subjects regarding study procedures and the investigational product. Detailed medication history was obtained from all enrolled trial subjects, which was followed by thorough clinical examination. Investigational product used for the study was the fixed dose combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg per tablet. Investigational product was provided to all the recruited trial subjects at no cost by the investigator and the investigational product was provided to the investigators by the sponsor. Trial subjects were asked to take the investigational product in the dose of 1 tablet twice a day for study duration of 5 days. Three visits were scheduled to determine the effectiveness and safety for the investigational product. Baseline visit was scheduled on day 1 where trial subjects were dispensed with the investigational product which was the fixed dose combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg per tablet and were instructed to take two tablets a day in the interval of 12 hrs for a total study duration of five days. Trial subjects were asked to visit clinical trial site on day 3 (visit 2) and day 5 (visit 3) considering the baseline visit (visit 1) as day 1 for the efficacy and safety assessment. Trial subjects were instructed to keep a diary to track their everyday symptoms and any adverse event that occurred. In case of serious or severe adverse event, the investigators were asked to remove the trial subject from the study and asked to give them the complete medical management till resolution of the adverse events.

Concomitant therapy

Other than investigational product, no pharmacological intervention or prescription was allowed during the study period. Non-pharmacological interventions such as cognitive behaviour therapy and yoga etc were allowed and encouraged during the study period.

Efficacy Assessment

The efficacy for the investigational product was calculated by measuring the decrease in the vertigo symptom score (VSS) over the study duration of 5 days. VSS was calculated over the vertigo symptom score scale where all the recruited trial subjects were asked to rate their all the vertigo related symptoms. The Vertigo symptom score scale was an eleven-point scale ranging from 0 to 10, with 0 denoting no symptoms and 10 denoting the most severe symptoms tolerated by the trial subjects. The VSS was further extrapolated with 4 grades showing the intensity of the symptoms experienced by the trial subjects, from no symptom to severe symptoms. Four grades were no symptom (0 on VSS), mild intensity (1-3 on VSS), moderate intensity (4-6 on VSS) and severe intensity (7-10 on VSS) symptoms.

Safety Assessment

In study duration of 5 days, all trial subjects were asked to keep a diary to record any adverse event if experienced and also in case of any significantly severe or serious AE, they were instructed to contact the investigator and discontinue the investigational product immediately. Adverse events were categorised as drug-related or non-drug-related adverse events after the causality assessment. Also, all the investigators were asked to provide the complete medical management to the trial subject in case of severe or serious adverse event or whenever needed.

Regulatory Matters

Manufacturing and marketing of the investigational product

has been approved in India. In India, the investigational product is classified as a schedule H drug. The informed consent form was read and signed by all of the trial subjects who were enrolled in the study.

RESULTS

A total 180 trial subjects were recruited for the study out of which 171 trial subjects completed the post marketing surveillance study. The average age of the trial subjects was of 49.2 years. There were 85 male and 86 female trial subjects completed the post marketing surveillance study. On day 1/ baseline visit, mean VSS was 6.69. On day 3 of the revaluation visit (V2), the mean VSS was reduced to 3.28, and on day 5 (V3), the final visit, it was further reduced to 0.87, almost half of the revaluation visit (V3). Figure 1 shows a graphical presentation of the mean VSS at every visit.

The percentage reduction in the mean VSS at visit 2 and 3 as compared to the baseline was 51.004 % and 86.986 % respectively. Graphical presentation for the percentage reduction in the mean VSS at visit 2 and 3 was as presented in the fig. 2.

The mean VSS was categorised into 4 different categories according to severity of symptoms. Trial subjects having VSS 0 did not showed any symptoms that means trial subjects were considered as recovered from the vertigo and considered in the category of patients with no symptoms. VSS 1-3 were considered as trial subjects with mild intensity symptoms and VSS 4-6 were considered as trial subjects with moderate intensity symptoms and VSS 7-10 were considered as severe intensity symptoms.

On day 1, baseline assessment revealed 67 trial subjects had

Adverse drug reactions	Number of episodes	Number of trial subjects	% of total population
Headache	7	4	2.29
Drowsiness	5	2	1.14
Sweating	3	1	0.57
Hyperacidity	1	2	1.14

Table-1: List of Adverse drug reactions reported during the study

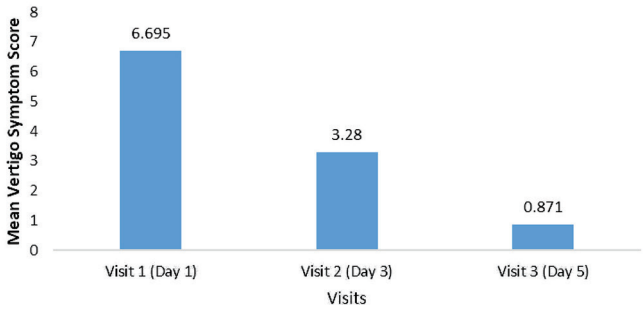

Figure-1: Mean Vertigo Symptom Score at day 1, 3 and 5

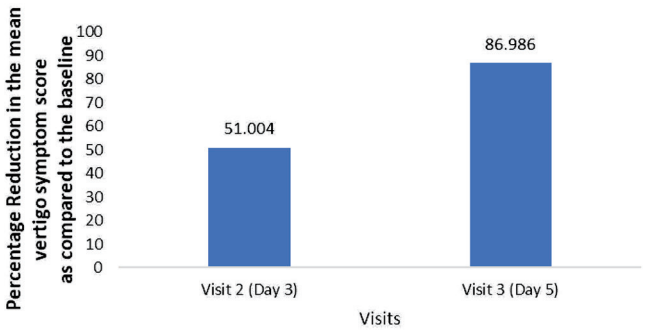

Figure-2: Percent Reduction in mean vertigo symptom score as compared to baseline

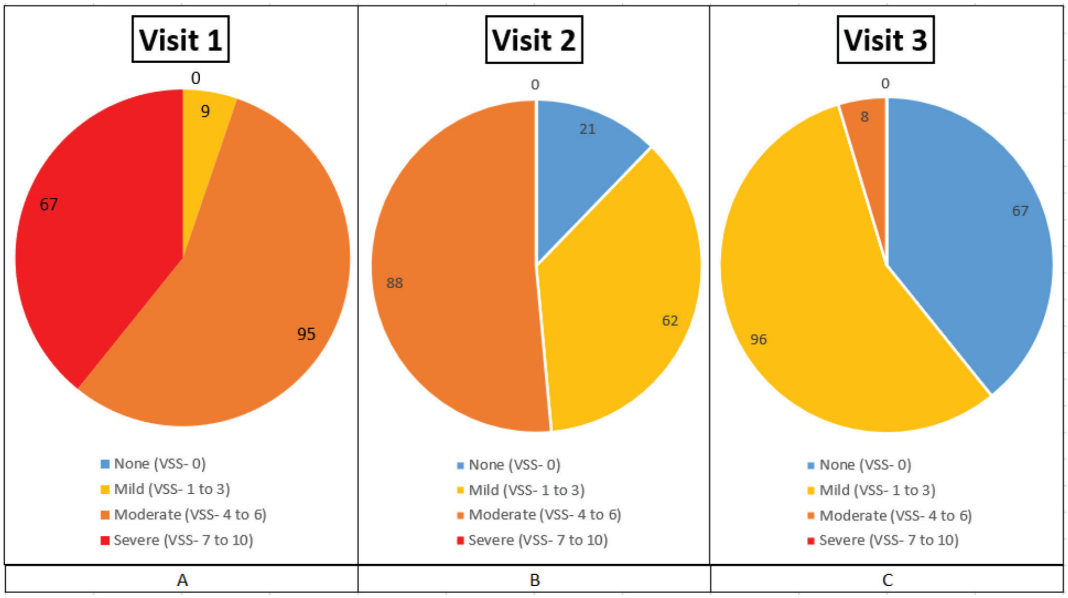

Figure-3: No. of trial subjects with no symptom, mild intensity symptoms, moderate intensity symptoms and severe intensity symptoms A) Visit 1 B) Visit 2 C) Visit 3

severe intensity symptoms of VSS 7-10. 95 trial subjects were found with moderate intensity symptoms and 9 trial subjects with mild intensity symptoms. Percentagewise at baseline severe symptoms were found in 37.18 %, moderate symptoms found in 54.97% and mild symptoms found in 5.26% of total population completed the study. On day 3, trial subjects were re-evaluated and found that 62 had a VSS score between 1-3, 88 had VSS between 4-6, indicating that 36.25 % of clinical trial subjects had mild symptoms and 51.46 % had moderate symptoms. At this visit, 21 trial subjects had no symptoms indicated by VSS 0 and no trial subject had severe intensity symptom. At visit 3, 96 trial subjects had VSS score 1-3 which showed that 56.14 % of the total trial subjects were having mild symptoms, 8 trial subjects had VSS 4-6 which showed that 4.67 % trial subjects had moderate symptoms. 67 clinical trial subjects out of total 171 clinical trial subjects showed VSS score 0 which reveled that 39.18 % trial subjects were completely cured on fifth day after administration of investigational product.

Safety Assessment

Total 16 adverse drug reaction of investigational product were reported by 9 trial subjects which are tabulated in table 1 below

DISCUSSION

Vertigo is an incorrect perception of movement or a feeling of the sense of motion when there is no motion in relation to the earth's gravity or movement in one's own body. Sweating, nausea, whiteness, and vomiting are typical autonomic symptoms of vertigo, since they are common in other forms of dizziness. Vertigo can be treated with antihistamines, calcium antagonists, histamine analogues (eg, betahistine derivatives), diuretics, neuroleptics as well as other psychotherapeutic medications, corticosteroids agents and hemorheologics. As vertigo is related to dysfunction of vestibular system in which homeostatic of calcium is disrupted and it also added with effects of histamine as well as cholinergic receptors. Hence combination of two antihistamines can be used to treat the vestibular dysfunction by inhibition of calcium influx and inhibition of histamine and cholinergic receptors. Cinnarizine, a selective calcium-channel blocker and dimenhydrinate, a H 1 antihistamine can be used in the treatment of vertigo.[13] This study was conducted to test the efficacy and safety for the fixed dose combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg per tablet for the indication of vertigo of various origin in Indian population. Total 180 trial subjects were recruited for the study out of which 171 trial subjects completed the study as per the study procedure and rest were lost to follow-up. The efficacy assessment was conducted by the efficacy assessment parameter- VSS. During the study, it was observed that VSS in all trial subjects was reduced during the post dose visits. Mean VSS reduced from 6.69 to 3.28 from visit 1 (baseline) to visit 2 which was on day 3 i.e., 51.004 % reduction as compared to baseline, and from 3.28 reduced to 0.87 in the next 2 days i.e. on day 5 which was a reduction of 86.98 % as compared to the baseline. The overall reduction in the symptoms of vertigo was 86.98% just in 5 days after the treatment of the investigational product was started to the trial subject. According to the above mentioned results, the investigational was beneficial for the treatment of vertigo for reducing the vertigo related symptoms. Total 9 (5.26%) trial subjects experienced 16 episodes of adverse drug reactions which were related to the investigational product including headache, drowsiness, sweating and hyperacidity. All adverse events experienced by the trial subjects were of expected, mild and non-serious nature. After the efficacy and benefit risk assessment, the investigational product can be considered as beneficial for the effective and safe treatment of vertigo in Indian patients. Below we have discussed some of the studies which were used as a reference during the conduct of this PMS study.

Joseph Pytel et al. performed a 4-week prospective, randomised, multicentric, double-blind, active-and placebo-controlled, parallel-group, outpatient study in men and women over 30 years old with central, peripheral or combination central and peripheral vestibular vertigo. The aim of this study was to compare the efficacy and safety of a combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg, as well as Cinnarizine 50 mg and Dimenhydrinate 100 mg monotherapy and placebo. The efficacy for the medication was measured using a five-point visual analogue scale (VAS) ranging from 0 to 4, with 0 suggesting no symptoms and 4 indicating the most extreme symptoms. Only trial subjects with a VAS score of greater than 1 and an irregular vestibulospinal moments pattern on craniocorpography were eligible to participate the study. The VAS scale was used to measure efficacy by using six vertigo symptoms. The study lasted four weeks and included 239 Hungarian patients. The VAS score of patients treated with a combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg was decreased by 1.37 points, from 1.85 to 0.45. The VAS score was decreased by 0.87 points in monotherapy with Cinnarizine 50 mg from 1.72 to 0.81. The VAS score was reduced from 1.69 to 0.87 in the monotherapy of Dimenhydrinate 100 mg, a difference of 0.83. Clinical trial subjects who were given placebo saw their scores drop from 1.74 to 1.01, a difference of 0.76. It was concluded in the study that the low fixed dose combinatoin of Cinnarizine 20 mg and Dimenhydrinate 40 mg was efficacious and safe as compared to others for the medical management of vertigo of central and/ or peripheral origin.[11]

Arne W. Scholtzat et al carried out a single-center, randomised, double-blind, parallel-group clinical study to compare the clinical effectiveness and tolerability of a fixed combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg versus monotherapy with the respective components of the combination for the treatment of acute vertigo symptoms caused by acute unilateral vestibular failure. The goal of this study was to compare the clinical efficacy and tolerability of a fixed combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg, as well as monotherapy with its respective components, in the treatment of acute vertigo symptoms induced by unilateral vestibular failure. The research was performed on 50 patients with acute vestibular vertigo for a span of four weeks, with each patient being advised to take one tablet three times a day in all cases. During

the first six days of service, all of the patients received a 15 percent mannitol infusion as part of routine treatment. The effectiveness of the medication was determined by measuring vertigo symptoms using a verbal rating scale (vertigo score) and vestibulo-ocular and vestibulospinal tests after 1 and 4 weeks of treatment. The combination therapy was more effective than 20 mg Cinnarizine ($P < 0.001$) or 40 mg Dimenhydrinate ($P < 0.01$) after one week of treatment. The fixed dose combination was also significantly more effective than Cinnarizine in reducing vertigo symptoms ($P < 0.01$) and significantly more effective than Dimenhydrinate in improving clinical trial subjects' standing balance ($P<0.05$) after 4 weeks. The combination therapy was found to be effective in 100% of clinical trial subjects, while Cinnarizine monotherapy was effective in 82.4 % of clinical trial subjects and Dimenhydrinate monotherapy was effective in 94.4 % of clinical trial subjects. No severe side effects were found in any of the clinical trial subjects. As a result, Arne W. Scholtz et al concluded that combination therapy was more effective than monotherapy in the treatment of vertigo.[12]

Kiran et al. performed 5 days open-labelled, multicentric, post-marketing surveillance study on Indian patients suffering from vertigo. The aim of the study was to corroborate the safety and efficacy for the fixed dose combination of Cinnarizine 20 mg and Dimenhydrinate 40mg. Efficacy was evaluated by improvement in signs and symptoms of vertigo to characterize and quantify the potential clinical benefits of this treatment. The reduction in vertigo symptom score (VSS) on the vertigo symptom scale was used to assess efficacy. The vertigo symptom scale which was used was an 11-point scale with 0 indicating no symptoms to 10 indicating the most severe symptoms. The study was completed on 168 trial subjects out of a total of 216 recruited. At baseline, the mean VSS was 7.277 which was reduced by 45.373 %, on day 3 to 3.975, and then it was further reduced by 86.426 % to 0.987 on day 5. Overall the symptoms of vertigo were reduced by 86.426 % in just five days. It was concluded at the end of the study that the fixed dose combination of Cinnarizine (20 mg) and Dimenhydrinate (40 mg) can be used for the medical management of vertigo.[13]

CONCLUSION

Fixed dose combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg per tablet was efficacious as well as safe for the treatment of vertigo in Indian population.

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DICLOSURE

This study was conducted as a part of pharmacovigilance activity for investigational product whose brand name is Vertidiz tablet which is a fixed dose combination of Cinnarizine 20 mg and Dimenhydrinate 40 mg per tablet which is marketed by Centaur Pharmaceuticals Pvt. Ltd.

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